Remarks

Rejection of the claims under 35 USC §113:

Claims 1, 3-4, and 6-7 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite. The basis for the indefinite rejection is the alleged use of a broad range or limitation, labile covalent bond in step b), with a narrow range or limitation, ph-labile covalent bond in step c). Applicants respectfully disagree. The covalent bond of step b), connecting the nucleic acid to the polyamine, is a distinct bond from the covalent bond of step c), connecting the carboxyl groups to amines. Because the terms "labile covalent bond" and "pH-labile covalent bond" describe different bonds and different components of the claimed invention, it is the Applicants opinion that the basis for the rejection is unfounded. Applicants request reconsideration of the rejection.

Rejection of the claims under 35 USC §103:

Claims 1, 3-4, 6-7, 10-13, and 15-20 have been rejected under 35 U.S.C. 103(a) as being anticipated by Wolff et al. (WO200075164) ('164) in view of Mathiowitz et al. (US 6,248,720) and Haines et al. (US 6,479,464). Applicants have amended the claims to clarify the differences between the instant claims and the prior art.

The Action correctly notes that '164 teaches at page 26 covalent attachment, via a labile bond, of a nucleic acid to a compound "that modifies the activity, function, delivery, transport, shelf-life, pharmacokinetics, blood circulation time in vivo, tissue and organ targetting, and sub-cellular targeting of the biologically active compound." It is the Applicants' opinion that the term '*modifies*' (at page 26 line 7) qualifies the nature of the compound and distinguishes the compound from the polycations and lipids described throughout '164.

The Action states that Applicants traversed this rejection, in their amendment of 14 October 2009, on the grounds that '164 teaches away from covalent attachment of nucleic acid to a polyamine. It was and remains the Applicants' opinion that the Examiner's assertion that a *complex*, as taught by '164, teaches or implies a covalent linkage between the components of the complex is incorrect. '164 does in fact teach that *complexes* involve *non-covalent* interactions (page 33 lines 9-12).

One skilled in the art would recognize that the field of '164 is DNA/polycation (or lipid) *complexes* and methods to enhance the functionality of DNA/polycation (or lipid) *complexes*,

as evidenced at: page 3 lines 19-24, page 7 line 18 to page 8 line 17, page 19 lines 31-33, page 20 line 6-8, page 20 line 16 to page 21 line 18, page 21 lines 15-18, page 23 lines 21-25, page 23 line 32 to page 24 line 1, page 33 lines 8-12, and page 33 line 33 to page 34 line 2.

"A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983)". '164, when taken as a whole, teaches that cationic polymers and amphipathic compounds (such as lipids and detergents, i.e. surfactants) can be used to deliver nucleic acids to cells *in vivo* and *in vitro*, and that this use is realized by *complexing* (Two molecules are combined, to form a complex through a process called complexation or complex formation, if the are in contact with one another through noncovalent interactions such as electrostatic interactions, hydrogen bonding interactions, and hydrophobic interactions. – page 33 lines 9-12 of '164) the polycation or surfactant with the nucleic acid.

This use of polycations and surfactants to form complexes with nucleic acid was well known in the art at the time of filing '164. '164 taught the use of pH-labile covalent linkages in modifying these polycations and surfactants in ways that improved their utility. '164 specifically teaches the application of labile covalent bonds in forming labile polycations and surfactants and modifying properties of polycations and surfactants, and in linking polycations to other polycations (caging) and non-nucleic acid polyanions (recharging) in electrostatic interaction with nucleic acid in nucleic acid complexes.

'164 also teaches, as the Action notes, that labile bonds may also be used to link nucleic acid to certain compounds. '164 specifically teaches modifying nucleic acid to attach reactive functional groups, cell targeting signals, and interaction modifiers such as polyethylene glycol or polysaccharides. These compounds collectively are able to *modify* activity and function (reactive functional groups), transport, shelf-life, pharmacokinetics, and blood circulation time in vivo (polyethylene glycol), and delivery and tissue, organ, and sub-cellular targeting (cell targeting ligands) (see page 22 lines 5-15). Neither covalent linkage of any polycation (or polyamine) to nucleic acid nor cleavage of a polycation from a nucleic acid is described or suggested in '164.

Even if taken in the broadest possible interpretation (broadest reasonable interpretation is the guiding principle of the MPEP), '164 merely teaches that any compound can be linked to the nucleic acid. In Takeda v. Alphapharm, 492 F.3d 1350 (Fed.Cir. 2007) the courts found that there is no *prima facie* obviousness found when the prior art teaches many compounds, only one of which, when modified, may lead to patentee's compound.

Further, '164 teaches as page 20 line 16 to page 21 line 18 that "these particles (poly-L-lysine/DNA or polyethylenimine/DNA complexes) are poor transfer reagents *in vivo* due to their toxicity and relatively stable interaction with DNA, which renders their complexation irreversible under physiological conditions." Covalent linkage, labile or otherwise, of these polycations to the DNA would, of necessity, further stabilize their interaction with DNA. One skilled in the art, knowing that stability of DNA/polycation complexes can inhibit in vivo transfection, would not have been motivated to further stabilize a DNA/polycation complex by covalently linking the polycation to the DNA.

Also at page 20 line 16 to page 21 line 18, '164 teaches "the present invention provides for the cleavage or alteration of a labile chemical group once the *complex* is in the desired environment," indicating that only polycation/DNA complexes are envisioned as nucleic acid delivery vehicles.

It is the Applicant's opinion that the instant invention involves new and novel combinations of components, using labile bonds and linking nucleic acids and reversibly modified polycations together in a manner neither taught nor suggested by '164. One skilled in the art, at the time of filing the instant invention, would not have been motivated to covalently attach the nucleic acid to the polycation.

Applicants further argue that '164 does not teach or suggest attachment of a nucleic acid via a labile bond to a membrane active polymamine *and* wherein the membrane active polymamine is *additionally* reversibly modified such that it becomes a polyanion. '164 does not teach attachment of a nucleic acid via a labile bond to a polyanion as is required by the instant claims (step (c) of claim 1, step (b) of claim 19).

The Action states that Applicant's did not address the combined teachings of the cited references, and reminds the Applicants that one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references.

However, the Action of 21 July 2009 states that Mathiowitz et al. but not Wolff et al. teaches polyvinylether polymers for transfection of nucleic acids into cells. The Action of 21 July 2009 also states that Haines et al. but not Wolff et al. teaches pardaxin peptide for disruption of cellular membranes. Applicants also note that, pardaxin, amino acid sequence GFFALIPKIISSPLFKTLLSAVGSALSSSGEQE (single letter amino acid code), has a molecular weight of 3395.9 daltons and therefore does not have a molecule weight greater that 10,000 daltons. Finally, the Action of 21 July 2009 states that it would have been obvious for one of ordinary skill in the art to modify the polymer taught by Wolff et al. with the polymers of Mathiowitz et al. or Haines et al. Thus, the Examiner has not combined Mathiowitz et al. and Haines et al. with Wolff et al. with respect to any aspect of the claims other than permissible polymers. Therefore, it is the Applicants' opinion that the Mathiowitz et al. reference is relevant only against claims 6 and 16 and is inappropriate against the other claims. Similarly, it is the Applicants' opinion that the Haines et al. reference is relevant only against claim 18 and is inappropriate against the other claims.

In view of the argument and amendments, Applicants request reconsideration or the §103 rejection.

The Examiner's objections and rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that claims 1, 3-4, 6-7, 10-13, 15-16, and 19-20 should be allowable.

Respectfully submitted,

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I hereby certify that this correspondence is being transmitted to the USPTO on this date: 2 April 2010 .

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